

# Countdown to a cure—the effort to finally defeat AIDS

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UCSF has assembled a team, led by Paul Volberding (second from right), MD, that is trying to eradicate AIDS disease forever. Credit: Steve Babuljak

The sun, barely penetrating the summer fog, dully illuminated the hallways of San Francisco General Hospital (SFGH) on July 1, 1981, as Paul Volberding, MD, started his first day of rounds and met his first patient as a UCSF faculty member. For Volberding, that day and that patient are unforgettable.

"He was a 22-year-old man with a strong Southern accent," recalls Volberding. "He was estranged from his family and completely alone." The patient was covered with the reddish-brown lesions common to Kaposi's sarcoma, a then-rare, slowly progressing cancer that usually afflicted elderly patients. "To see this young man with disseminated Kaposi's, it was just striking – a very unusual situation," he says.

Despite extensive interventions, the man died quickly from multiple infections. "Medically, he was amazing and challenging – but socially, too. Even our most disconnected and marginalized patients often have someone present to help."

Soon after, Volberding's rounds were filled with dying young people. "That first case told us where we were going to be for the next 30 years," he says.

## **At the Epicenter of an Epidemic**

That first patient inspired Volberding to begin the search for a cure to what soon became known as acquired immune deficiency syndrome (AIDS). AIDS is caused by the human immunodeficiency virus (HIV), a retrovirus that attacks the immune system. Volberding, director of the AIDS Research Institute and director of research for Global Health Sciences, came to UCSF in 1978 as a medical oncology fellow and researcher in the virology laboratory of Jay Levy, MD, who co-discovered HIV in 1984. Volberding left Levy's lab to take the clinical job at SFGH (now Zuckerberg San Francisco General), not realizing that he was leaving a retrovirus laboratory to work in the middle of a retroviral epidemic.

With the outbreak rapidly expanding, Volberding and his colleagues were spread thin as the number of sick and dying patients increased daily, and haunting photos of skeletal young men filled the media. "It

was a death watch," says Jay Kerzner, a longtime patient of Volberding's who was diagnosed with HIV in 1986. "People were just wasting away."

In a time when gay men experienced open discrimination, hospitals also turned away patients out of fear and incomplete knowledge. Instead, Volberding stepped into the center of the maelstrom. His wife, Molly Cooke, MD, also worked in the middle of the epidemic as the hospital's then-chief resident in medicine. Despite waking in a sweat from recurring nightmares about passing the virus to their young children, Volberding and two of his SFGH colleagues – Donald Abrams, MD, and the late Constance Wofsy, MD – founded one of the nation's first AIDS-designated clinics in Ward 86 at SFGH. They also developed the San Francisco Model, a comprehensive treatment model emphasizing compassion and respect and encompassing social services, which was soon emulated around the globe. In the face of growing fear of the virus, they accepted all patients who needed treatment, regardless of their means.

Volberding's dedication has never ceased. Widely considered one of the world's leading AIDS experts, he has worked on clinical trials for HIV-related malignancies and antiretroviral therapies (ARTs) and has supported research by other UCSF faculty members, who now investigate HIV/AIDS in more than 60 countries. He also co-directs the UCSF-Gladstone Center for AIDS Research. Ward 86 is now considered one of the top-rated medical care facilities for AIDS in the world, and the World Health Organization recently endorsed the San Francisco Model as the minimum standard for HIV care.

Today, Volberding is tackling what may be his toughest task yet: leading a team trying to eradicate the disease forever.

## **Shrewd Virus Still Infecting Millions**

Although the global HIV pandemic has claimed an estimated 39 million victims, the advent of ARTs slowed the progression of the disease. HIV attacks the immune system, specifically its CD4 cells (T cells), making the body more likely to succumb to infection. ARTs have been highly effective at keeping the virus from infecting new cells in HIV-positive individuals. But as soon as a patient goes off ARTs, HIV bounces back, giving evidence the infection hibernates within the system. AIDS was initially considered a disease affecting homosexuals, sex workers, and IV drug users. "They called it the 'gay cancer,' says Kerzner, referring to the early days of the epidemic.

But the face of AIDS has changed. HIV now infects mostly women and children. Women are twice as likely to acquire HIV during intercourse and today account for more than half of all people living with HIV. Despite all we know, in 2014 alone there were roughly 2 million new infections globally, 220,000 of which were of children infected by HIV-positive mothers. Seventy percent of the global HIV-positive population lives in sub-Saharan Africa, where people often must walk for a day or more to reach public transportation to treatment centers. More than 60 percent of those infected cannot afford treatment or are far from a treatment facility. Their plight makes clear the need for a safe, economical, orally administered, and transportable cure.

Driven by a sharper understanding of the nature of HIV infection and a growing population without access to care, many international AIDS organizations have launched concentrated programs to end AIDS. "We are at a unique moment in history. Over the next five years we have a fragile window of opportunity to shift gears and put the global HIV response firmly on the fast-track to end the AIDS epidemic," Michel Sidibé, the executive director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), recently declared.

## **Quickening the Pace**

Fully aware of the challenges ahead, the Foundation for AIDS Research (amfAR), which focuses on accelerating cure research by breaking down traditional barriers, launched its "Countdown to a Cure for AIDS." The initiative is strategically investing \$100 million in uncovering the scientific basis for a cure by 2020. The strategy looks not only at the brilliance of the science but also at the excellence of the collaboration.

Interested in finding the best team to uncover a cure, amfAR invited qualified individuals to submit proposals for funding. Among those invited was a San Francisco-based, self-assembled, multidisciplinary team of world-class scientists, clinicians, and industry experts with a phenomenal combined history clinically and in the lab. Many of the individuals have collaborated on HIV cure research for more than three decades. The team includes specialists from UCSF, the Gladstone Institute of Virology and Immunology, the Blood Systems Research Institute, Gilead Sciences, the Infectious Disease Research Institute, and other academic and industry partners.

On World AIDS Day 2015, December 1, amfAR revealed the cornerstone of its initiative: the establishment of the amfAR Institute for HIV Cure Research, led by Volberding and based at UCSF's Mission Bay campus. "The potential for this team of researchers to develop a cure is unparalleled" says Rowena Johnston, PhD, vice president and director of research at amfAR.

amfAR awarded the team \$20 million to begin its investigations. HIV is adept at concealing itself within the body, making it harder to eradicate, so the team's main objective is to harness the power of the innate immune system to push the virus from its hiding places and eliminate or control the virus once it has revealed itself – a strategy referred to as "Shock and Kill."

amfAR identified four key scientific challenges – charting,

understanding, recording, and eliminating (CURE) – which constitute a research roadmap of barriers to an HIV cure and also represent the four modules of the institute's research focus. Each of the four research modules has a specific purpose within the effort to locate, shock, and kill HIV wherever it is hiding.

HIV stealthily infiltrates and hides within the body, confounding researchers with its game of hide-and-seek. The Charting module seeks to identify and chart the "safe houses" where HIV hides, even in the presence of suppressive ARTs. Charting researchers will figure out which organs harbor the virus, in which cells and at what stage the virus hides, and whether these hiding places vary by gender. Using tissue samples, the team will then determine whether the virus found is "replication-competent." Although HIV reproduces at alarming rates, up to 90 percent of the viruses in infected cells have mutations or deletions, making them unable to infect other cells. However, even incompetent HIV cells produce inflammation and compromise immunity.

Capitalizing on that inflammation and then stimulating a T-cell response in an attempt to find an interaction that reduces toxicity yet allows for destruction of the hidden HIV reservoir, is the work of the Understanding module. Encouraging the inflammation in a way that is therapeutically meaningful without harming the patient is essential. "We are right on the knife's edge. Too much stimulation can produce a toxic effect. Not enough, and we don't rouse the virus out of its slumber," says Warner C. Greene, MD, PhD, a professor of medicine, microbiology, and immunology at UCSF and the director, senior investigator, and Nick and Sue Hellmann Distinguished Professor of Translational Medicine at the Gladstone Institute of Virology and Immunology. With the majority of HIV viruses being defective, unveiling the lingering sleeping viruses that are able to spread is crucial.

Using the immune response as a map, the Recording module will locate

and determine the size of the dormant HIV reservoir by focusing on evolutionary and genetic insights to gauge the size of the reservoir and determine how it can best be destroyed.

The Eliminating module hopes to lure the virus out of hiding by stimulating toll-like receptors (TLRs). The TLR class of proteins plays an important role in the immune response and the body's ability to recognize invading pathogens. With data from Gilead Sciences indicating that stimulating TLR-7 pushes HIV out of hiding and increases the effectiveness of vaccines, this module is focused on manipulating TLR-4, TLR-7, and TLR-9 to test the shock-and-kill curative hypothesis in preclinical and, eventually, human trials.

## **Collaborating for a Cure**

The ambitious five-year timeline means the CURE team will need to take risks and push boundaries, working closely to inform next steps in the discovery of a cure – a cure that would fundamentally change the lives of tens of millions of people and end one of the worst infectious disease epidemics in human history. "HIV research has evolved from a process of discovery to a technological challenge," says amfAR's Johnston. "And now it's reached a critical mass. Bringing powerful new technologies, brilliant minds, and financial resources to bear, we believe it's a challenge we can overcome."

With the potential to help so many, the amfAR team is poised to discover the scientific basis for a cure. "UCSF has been there right from the beginning of HIV," says Volberding, who holds the Robert L. Weiss Memorial Chair for HIV/AIDS Research. "We've been committed to this epidemic for a long time, many of us collaborating as a team for decades. Now we are bringing it full circle and coming together to find a cure. It's a great UCSF story!"

Patients whose lives were changed by the advent of ARTs are also feeling a glimmer of hope. "What would a cure feel like? After a 30-year struggle with this disease myself . . . I wish it had come earlier," says long-term survivor Kerzner. "But I can't even think about a cure without remembering so many lives cut short by HIV. It would mean the end of a very dark era. A cure would mean a more hopeful future for so many people around the world."

Provided by University of California, San Francisco

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